ISSN : 0974-2700
Volume 5
Issue 2
Apr-Jun 2012

Journal of Emergencies, Trauma, and Shock

Synergizing Basic Science, Clinical Medicine, & Global Health

Official Publication of INDO-US Emergency and Trauma Collaborative

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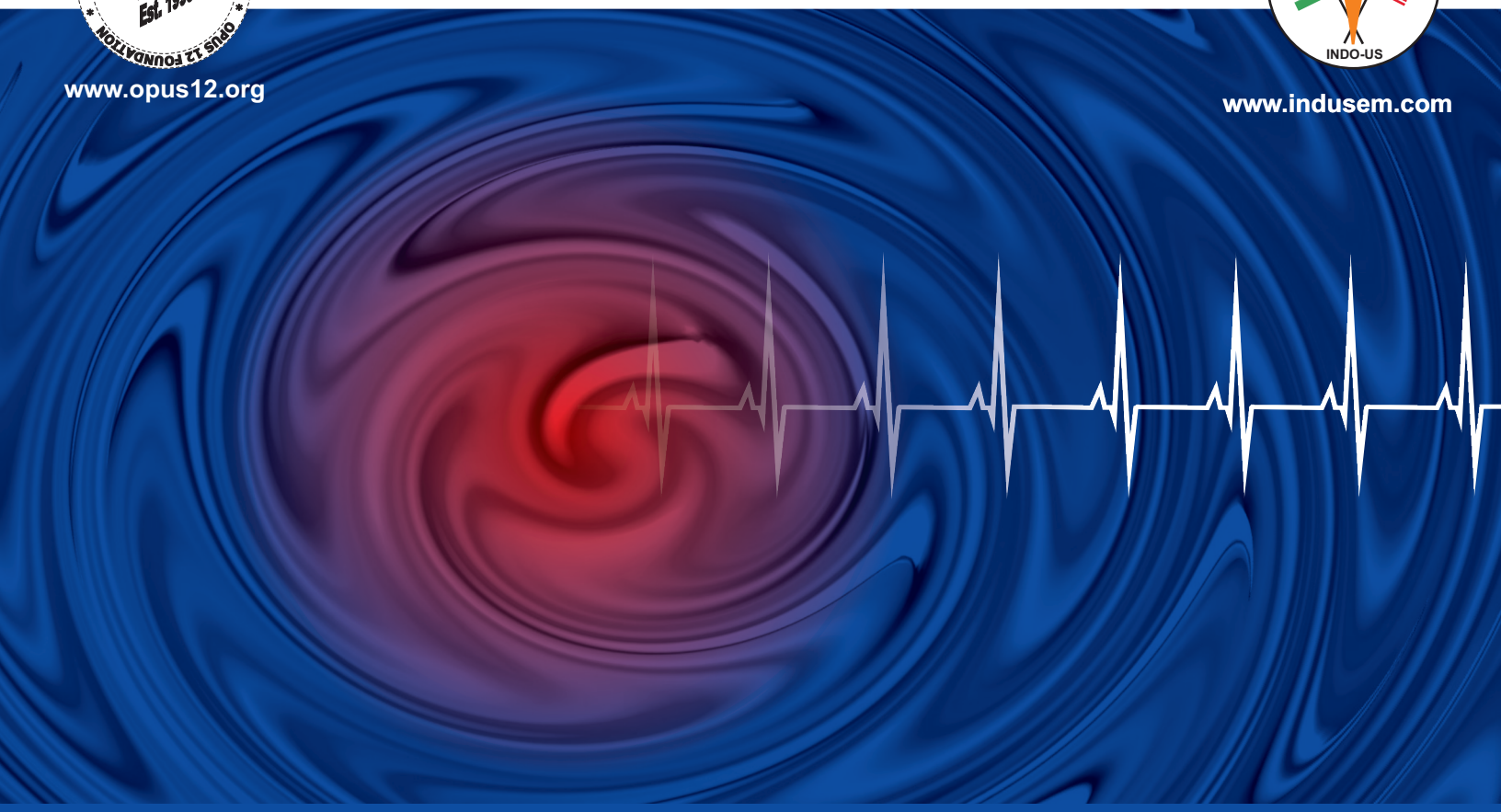

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Editorial

What's new in Emergencies Trauma and Shock? C-reactive protein as a potential clinical biomarker for influenza infection: More questions than answers

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Influenza viral infection is a common and potentially fatal respiratory infection, particularly when the inflicting strain is an antigenetically novel strain that can result in severe manifestations (e.g., recent H1N1 epidemic). C-reactive protein (CRP) is a classical acute phase protein that is extremely sensitive but non-specific biomarker in many systemic inflammatory processes.[1]

Discovered in 1930, CRP was so-named because it was first found to have reacted with the C-polysaccharide of cell walls of pneumococci to form precipitate.[2] Physiologically, this pentameric protein secreted from the hepatocytes is an important component of the innate immune response to inflammation and infection. By binding to phosphocholine, polysaccharides, and peptidopolysaccharides found in bacteria, fungi, and parasites, it activates the classical complement pathway through C1q, binding directly to the Fc portion of IgG, stimulating releases of IL-1 and TNF-α in macrophages, and thereby, enhances phagocytosis of foreign substances.[1]

In this issue, the authors of the article *Correlation of C-reactive Protein to Severity of Symptoms in Acute Influenza A Infection* demonstrated a correlation between the severity of influenza symptoms with the initial CRP level. In that study, patients with symptoms suggestive of influenza were screened with Enzyme-Linked ImmunoSorbent Assay (ELISA). Patients suspected of having bacterial infection or concurrent bacterial infections were excluded. It was shown that patients with CRP values greater than 25mg/L had an average symptom duration that was significantly longer (13.44 days) than those with a CRP less than 25 mg/L (8.18 days). These findings are consistent with the results from a previous study.[3]

But do these findings mean that we are nearer to using CRP in routine clinical practice for the diagnosis and monitoring of the progress of influenza infection?

Firstly, CRP by itself, although highly sensitive, is non-specific for many inflammatory diseases including bacterial and to a lesser degree, viral infections.[4] The non-specific property of the acute-phase protein renders CRP a low discriminatory value for diagnostic purposes, especially in an emergency department.

Inflammatory mediators such as tumor necrosis factor and interleukins stimulate hepatic synthesis of CRP.[5] CRP in turn, induces tissue factor expression by monocytes, thereby increasing procoagulant activities.[6] In fact, this is probably one of the reasons why increased levels of CRP is associated with increased risk of coronary thrombosis and cerebrovascular thrombosis.[1,3]

Generally, CRP level in a healthy person is usually lower than 10 mg/L, although higher levels can be found with increasing age. There is no difference in mean concentrations between men and women although higher levels are found late in pregnancy. This increase in CRP usually takes place in the first 6 to 8 h and can reach peak levels approaching 350–400 mg/L after approximately 48 h.[7]

On the other hand, once the inflammation resolves, the CRP level rapidly declines too with an elimination half-life of about 4 – 9 hours.[7] While a non-specific marker, this property of rapid rise and fall in tandem with the progression and decline of infections gives CRP an advantage point as a marker for disease activity.[7] As mentioned, viral infections and any mild inflammation elicit a smaller increase in CRP level (10–40 mg/L), while bacterial infection as well as active inflammation can elicit much higher responses of between 40–200 mg/L. In some severe bacterial infections and burns, the level can increase more than 200 mg/L.[7]

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Access this article online

Quick Response Code:

Website: www.onlinejets.org

DOI: 10.4103/0974-2700.96477

Nonetheless, severe infections itself is prothrombotic.[8] For example, exposure to bacterial endotoxins triggers release of various inflammatory cytokines,[8,9] particularly tumor necrosis factor α, interleukin-1β, and interleukin-6. These cytokines are capable of activating coagulation and inhibiting fibrinolysis, and the procoagulant thrombin is capable of further stimulating multiple inflammatory pathways.[9] Eventually, all these pathways lead to widespread endothelial injury, resulting in further microthrombosis, and thus, adding more confusion to this conundrum. In other words, although the high level of CRP may be due to severe influenza infections, but perhaps, a severe infection itself triggers a more extensive thrombosis, and this thrombosis itself is a triggering factor for the higher CRP level.[10] Is the high level of CRP due to the infection severity itself or it is because of associated thrombosis? Furthermore, CRP causes further thrombosis by inhibiting fibrinolytic activities and inducing plasminogen activator inhibitor-1 (PAI-1) release from endothelial cells.[10]

Arguably, however, one might say that other non-specific markers have also been used successfully and indispensably for certain infections, for example, platelet counts for dengue fever. But in such cases, the biomarker abnormality is a specific feature of the infection itself, rather than just an association. The primary question we need to explore therefore is whether CRP abnormality a specific feature of influenza or it is just an association.

Second, influenza is such a common and self-limiting disease that it is impractical to investigate every cough and cold cases. In fact, we often do not routinely do specialized laboratory investigations to differentiate bacterial from viral origin of a patient with upper respiratory tract infections other than relying on clinical cues: if the symptom duration persists longer than the first 5–7 days, a bacterial origin should be suspected. In fact, in this current study, the authors have to take every measure to ensure that the etiology of the patient's symptoms is not due to a bacterial or concurrent bacterial origin other than the influenza itself. Furthermore, to specifically pinpoint to influenza A virus requires either viral culture or in this particular study, a positive ELISA assay for influenza A antigen. In many laboratories around the world, these specific tests are not readily available, are too costly for routine testing, or not available easily as a bedside investigative tool in emergency departments or wards. As such, it is not a cost-effective measure to diagnose influenza A unless an epidemic of a novel influenza antigen has emerged again as an outbreak.

Other questions that should be addressed include: Does this increasing trend in CRP occur specifically in influenza A? How about the trends in other viruses? How do we differentiate them? In a study done previously, both rhinovirus and influenza virus cause increase in CRP.[11] In fact, previous studies have shown that most viral infections are associated with a modest CRP elevation of about 20 to 40 mg/L, although greater elevations of more than 100 mg/L may occur in infections caused by adenovirus, influenza, measles, mumps, and varicella.

Even if a biomarker were to be used routinely to monitor the progress of influenza infection, is CRP the most suitable choice? In a comparative study on the trend of CPR versus that of serum amyloid A (SAA) protein in experimental inflammation, it is shown that the increase of CRP was less marked as compared to that of SAA, suggesting that SAA may in fact, be a more sensitive marker.[11]

Nonetheless, because of its rapid rise and fall in relation to the severity of inflammation, CRP is probably a better marker than erythrocyte sedimentation rate (ESR). While CRP level returns to normal quickly upon resolution of the inflammatory insult, ESR level may not return to normal for several weeks despite clinical improvement.[7] Furthermore, the CRP levels are not affected by anemia, polycythemia, protein level, etc. It is also minimally affected by the patient's age as well as gender.[7] On the other hand, these factors mention can affect the ESR level.[7]

As such, albeit non-specific, CRP has been used as a biomarker for the inflammatory diseases such as appendicitis, cholecystitis, pancreatitis, pelvic inflammatory disease, pneumonia, urinary tract infection, and meningitis.[7] Still, another question that need to be conclusively answered is whether the different types of influenza viruses elicit varied degree of CRP response. Influenza viruses are notoriously known to have show great antigenic diversity. Of the three types of influenza viruses—A, B, and C—only types A and B cause widespread outbreaks.[12] Is CRP, therefore, a sensitive marker for influenza A and B only? Is there any difference between these two responses?

Influenza A viruses are further classified into subtypes based on antigenic differences between their two surface glycoproteins, hemagglutinin and neuraminidase. There are approximately 15 hemagglutinin subtypes (H1–H15) and nine neuraminidase subtypes (N1–N9) for influenza A viruses. Viruses of all hemagglutinin and neuraminidase subtypes have been discovered from aquatic birds, but only three hemagglutinin subtypes (H1, H2, and H3) and two neuraminidase subtypes (N1 and N2) have stable lineages in the human population.[12] Does CRP elicit different responses in all these different subtypes?

Perhaps CRP is a more useful marker for neonates. Previous studies have shown that CRP is the single best biomarker in early detection of neonatal septicemia, and that serial measurements correspond to the course of the infection, particularly after the first three day of life. In neonates, CRP is also a useful marker to monitor for the efficacy of antibiotic treatment.[7]

As a whole, the results from this study represent yet another step towards exploring further uses of this ubiquitous biomarker. But perhaps, at this stage, it is more appropriate to say that CRP does correlates with the severity of viral infections in general, rather than specifically for influenza A infection. Secondly, perhaps measuring the trend of serial CRP level is more useful than the absolute level itself. Nonetheless, influenza, being such a common infectious disease, is self-limiting in most cases. Unfortunately,

it can also vary from symptomless infection to the most severe course of illness, and in some cases, death. Furthermore, specifically within the context of pneumonia, CRP is not useful for discriminating between bacterial and viral infections although as mentioned earlier, the increase in response of bacterial infections is generally bigger than that of viral infections.[7] In this regard, for lung infections, CRP is found to be useful marker more as a guide to monitor response to antibiotic treatment as well as monitoring for the development of complications. In other words, although higher CRP levels usually correspond to bacterial pneumonia, especially due to *Streptococcus pneumoniae*, the ED management should be based on traditional parameters and clinical assessment rather than on the CRP level. In fact, there is no data to suggest that CRP is a better prognostic indicator than clinical indicators secondary to pneumonia. Nonetheless, an elevated CRP level greater than 100 mg/L often indicates treatment failure.[7]

In conclusion therefore, the ultimate question is not whether CRP can be used to monitor the progress of infection, but rather, the question is should it be used, and even if it should be used, when it should be used.

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How to cite this article: Chew KS. What's new in Emergencies Trauma and Shock? C-reactive protein as a potential clinical biomarker for influenza infection: More questions than answers. J Emerg Trauma Shock 2012;5:115-7.

Received: 02.12.11. **Accepted:** 01.01.12.